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QUININE PROPHYLAXIS FOR MALARIA.

By H. R. CARTER, Senior Surgeon, United States Public Health Service.

Among the methods of preventing malarial fevers (chills and fevers, bilious fever) the use of quinine ranks high. It is not so good a method as getting rid of malaria-bearing mosquitoes where this can be done economically, but in many communities this is impracticable, at least for the present. It is not so good as good screening carefully watched, but this, too, will not be used generally in rural communities. Frequently it can not be.

The use of quinine to prevent malaria is practicable now everywhere and by almost everyone, and it is efficacious. A farmer may not be able to drain and clear his land so as to get rid of mosquitoes. He may not be able to screen his house and keep his screens in order, but he will always be able to buy the amount of quinine which will protect his family from fever, especially as it may take no more to prevent fever than it would to cure it; maybe less.

The use of quinine to cure malarial fevers has been known for a long time and its use for this purpose is very general. It has been used to prevent them also for quite a while (the first notice that I have of it is in 1847) and of late years has been extensively so used, but nothing like so generally as its use to cure. It has been used systematically since 1902 by the Italian Government to prevent malaria, not much at first, but increasing its use as its good effects were seen. What the results were we shall see later. So good were they in Italy that its use as a preventive extended to other countries similarly situated; i. e., highly malarious farming countries. Greece, Algeria, and a number of other countries have tried this method and with good results.

It is nowise unknown in our Southern States. Dr. McMullan, of Elizabeth City, N. C., told me that when a young man—when malaria was far more severe in North Carolina than it is now—he had four attacks of what is known there as hemorrhagic malarial fever (the "blackwater fever" of the British writers) and that he had felt pretty sure that if he had another it would kill him. As he suffered every year from malarial fevers he had thought his chance of

another attack (of blackwater fever) good the next season. He began then and for a number of years took 5 grains of quinine a day, from the beginning of summer until November. He had no more chills or fevers. He took these small doses of quinine to prevent another attack of blackwater fever and escaped both it and the chills and fever which he had been accustomed to having. Capt. Laughinghouse, of Greenville, N. C., tells me that when he took charge of the convicts of the State malarial fevers had been very prevalent and very severe among them every year and that before the sickly season began he had a number of pills made containing, among other things, $2\frac{1}{2}$ grains of quinine each. One pill was taken twice a day by each man. The convicts were, for the years he had them, the freest from fever of any body of people of the same number in the community. Miss Margaret Brown, of George, N. C., by the systematic use of quinine as a preventive has greatly lessened the malaria among the school children at that place. Her results are reported as excellent. She is, I think, the first in North Carolina who has systematically tried to follow the Italian method of quinine prophylaxis and deserves the credit of a pioneer.

This method can probably be used in any community anywhere in the United States. It has been used successfully to a small extent. Let us see, then, whether it should be used generally and, if so, what its use promises.

First, we must see if it is efficient and whether it can generally be depended on to prevent malaria. If it is only occasionally successful it isn't worth trying.

Second, we must see if taking it in the doses and for the long time necessary for success does harm to those taking it. If so, it may not be advisable to take it—depending on how much harm it does.

Third, we must see whether it causes much discomfort.

(1) *Is quinine efficient to prevent malaria?*—Giving a small number of instances like those I have cited is not convincing because we know that with some people chills stop of their own accord; that in some years fevers are less prevalent than in others, and my instances may have been of such people or have fallen in such years. Fortunately there is an experiment on a scale so large and continued for so long a time that errors from chances of this kind are eliminated.

Italy is a country which has been malarious—much of it highly malarious—for some centuries. In Italy quinine has been used systematically as a preventive, at first on a small scale and then on a large one, for the past 10 years, and this was the only measure to prevent malaria which was used for the people we would consider, the farming people of Italy. Also a fairly accurate account was kept of the amount of malaria before and after the use of this preventive measure. The record of deaths especially runs back many

years and was very accurately kept. It seems, then, if the results in 10 years' trial, over a large country with as bad or worse malaria than the United States, show a large diminution of the disease then this method should be efficient in the United States also.

The Government of Italy, in 1902, began the sale of quinine at cost price to communes and towns, which agreed to distribute it gratuitously to those unable to purchase it. In 1903 these political units, towns, etc., were obligated to issue it gratuitously to poor people for prophylactic use. In 1904 it was ordered to be given to all working people for use in this way.

Now as to the results. Dr. Celli's statistics, from which all that follows is taken, give the average number of deaths per year for the 10 years preceding 1902 in all Italy as 14,048. For the nine years following 1902—i. e., 1903 to 1911, inclusive—the average number of deaths was 5,435—between one-half and one-third of the other. If we take the average of the last five years, we have only 3,853 deaths—not much over one-fourth of the former number. This comparison of the death rate ought to indicate some of the change that has taken place in the malarial conditions in Italy since quinine prophylaxis has been used. Let us look at statistics showing the change in the prevalence of the disease—that is, the number of cases. The number of patients from the Agro Romano, a very malarious district outside of Rome, treated in 1900 was (Celli again) 11,653. Some quinine was used in this district in 1901 and the number fell to about 8,000, but for the nine years ending in 1911, during which it was systematically given, the average number of cases was 3,603; for the last five years, 2,974.

Now compare these figures: The deaths from malaria in Italy reduced from 14,048 per year to 5,435 per year and then to 3,853 per year for the last five years. The cases of fever from one section reduced from 11,653 per year to 3,603 per year and then to 2,974 per year for the last 5 years.

There is no question that there has been a very great diminution in the amount of malaria among the farming people of Italy since the introduction of quinine prophylaxis. As no other means have been taken to prevent malaria among these people this reduction must be ascribed to the quinine taken as a preventive. Note, too, that it is a progressive reduction—increasing as the people learn its value.

The Italians living in malarial districts do not all take the quinine. To do so is not compulsory. It is simply offered them free, and if one may judge by our experience on the Isthmus it is taken rather freely where malaria is bad and very little where it is mild. If the quinine taken made the diminution shown, that diminution would have been greater had the quinine been taken by everyone.

This is shown in the penal agricultural colony at Castiadas, where the quinine was given under orders. The cases of malaria in 1904, 1905, and 1906, when no quinine was given for prophylaxis, were 76 per cent of the force. In 1911—after four years use—there were 5 per cent—less than one-fifteenth as many. So in the Army—where men are under discipline and quinine is taken under orders. In 1902 the attack rate of malarial fever in the Army was 27.5 per cent; in 1911 it was 4.9 per cent of which over 3 per cent were relapses of old cases.¹ These last two show what can be done by quinine in the prevention of malaria.

Similar results are reported from Greece and Algeria, but figures would simply repeat more or less what is given for Italy. The use of quinine has been successful at Lagos (McGregor), Brazil (Chagas), and Demarara (Ozzard), and other places. In Formosa and German East Africa as good results have been obtained by the Japanese and Germans, respectively, although using a different method of administration. I think, then, we may claim that quinine used as a preventive will greatly lessen the number of cases of malaria.

(2) *Used as a preventive, is quinine injurious to those taking it?*—No such effects are reported from Italy or Greece, or any other place where it has been used extensively and for a long time. In Panama, before the reduction of the malarial mosquitoes or the screening of the houses, many, I think most, of the Americans took three 2-grain tablets of quinine daily for the first two or two and one-half years. This was done the whole year, for the malarial season there is 12 months, and there was no report or complaint of injury caused by the practice. It was not done universally—but it was very generally done by the higher officials. The quinine was passed around at the mess tables at Ancon Hospital as regularly as the biscuits, and there practically everyone took it.

It was claimed on theoretical grounds that when those who had been taking quinine in small doses did develop malarial fever they would be much harder to cure because the malarial parasite would have become accustomed to quinine. However this may be in theory, I can find no evidence for it in practice. Indeed, Celli states that "such fevers as occur are milder and more readily curable by simply increasing the dose of quinine to the usual curative dose." They certainly are milder.

Will it induce blackwater fever? That the Italian death rate falls from 14,000 to less than 4,000 seems rather to negative that. With few exceptions all the men who have reported the diminution of malaria from the prophylactic use of quinine also report the diminution or disappearance of blackwater fever. None report any

¹ In spite of the implication that quinine prophylaxis was the only antimalarial measure used, it seems improbable that such adjuvants as were available were not also used for the Army.

increase of it. And this, although they recognize the effect of quinine in precipitating an attack of this disease. Even those who do not regard blackwater fever as of malarial origin assert "the prophylaxis of malaria prevents the development of blackwater fever." (Leishman et al.)

(3) *How much discomfort does the taking of quinine cause?*—Here one can not be so positive. Some people bear quinine less well than others. A few can not take even a very small dose. In general, however, the dose proposed by the Italians—equivalent to from 5 to 7 grains of the sulphate per day—can be taken without discomfort. Some can not take this amount without discomfort, yet my own observation is that one frequently becomes accustomed to these doses of quinine, and, after persevering for say a week, can take them without trouble even when they were annoying at first. The salts that are least soluble seem to be the best borne—thus the sulphate is better borne than the bisulphate and the tannate best of all. This last, however, is weaker in quinine than either of the others. One grain of sulphate has about the same quinine content as $2\frac{1}{2}$ grains of the tannate. The writer is unusually susceptible to quinine, yet he found little difficulty in accustoming himself to the doses taken on the Isthmus and no discomfort after he was so accustomed. The tannate he has never tried.

We have seen that the use of quinine as a prophylactic lowers the malarial sick rate and death rate. That is proven. Does it prevent the infection of the individual or simply the development of the infection into a malarial attack? If the former, one need take it only when exposed to malaria; that is, in a malarial country and during the malarial season. If the latter, one may be infected with malaria, although the attack is prevented from developing by the quinine. If he stops the quinine then, even when no longer exposed to malaria, he may develop an attack from the infection present. The latter has been the case often enough to show that in many cases the quinine is able to prevent the development of an attack from an infection which itself it did not prevent. On this account it is advisable not to stop the use of quinine immediately on the advent of cool weather or on leaving the malarial district, even if one has not had any malarial fever while taking it. To continue the quinine for awhile—a month or several months—until it and one's natural resistance can overcome the infection is good practice.

From the last paragraph the question at once arises: Are those free from malarial attacks on account of taking quinine infective to mosquitoes? Some of them certainly are. Malcolm Watson, as quoted by Ross, Ozzard and others have found a number of "carriers" among such people—in one place 20 per cent of those examined—only a small number examined, however. Observations on

a large scale are needed on this subject, and Italy would seem a peculiarly favorable place to make them. Yet, since the way quinine prevents the development of malarial fever is almost certainly by keeping the number of malarial parasites below the number necessary to produce an attack, the chance of any such (quinine-protected) person being a source of infection to mosquitoes would be lessened by *approximately* the proportion in which the number of parasites is lessened. Some, too, doubtless, would not become infected. The result would be then that those protected from attack by quinine prophylaxis would be less apt to be a source of infection to mosquitoes than if they had not taken it; some would not be infected at all and others would harbor far fewer parasites. This also lessens the amount of malaria in the country. As malaria lessens, prosperity increases from the increase of strength and energy of the people, and with increased prosperity comes land better cleared and better drained, screened houses and better hygiene generally; an endless chain of betterment.

It is only in this way—by quinine prophylaxis leading to anti-mosquito work—that permanent results can be obtained from it. In spite of it there will always be persons infective to mosquitoes, some among those who take and are protected by quinine, but a much larger proportion among those who do not. So when these measures are discontinued the original conditions of malaria will prevail.

One word should be said as to the administration and dose of quinine as a preventive of malaria. There are two principal methods of administration; the one canonized by Koch—large doses at considerable intervals; the other, smaller daily doses as used in Italy. In the first method 16 grains are given daily every ninth and tenth day, or eighth and ninth day, or even seventh and eighth day if malaria be very prevalent. There are various modifications of this—smaller doses at less intervals, as 8 grains every five days or twice per week. This method and its modifications have been eminently successful in the very malarious districts of German West Africa and also in the hands of the Japanese in Formosa. The dose regarded as proper by the Italian sanitarians is equivalent (in quinine content) to about 5 to 7 grains of quinine sulphate for adults given daily and half that amount for children under 10. For the latter they especially recommend the tannate of quinine in 5-grain doses—(2 grains of sulphate about)—made up into chocolates. This is said to be pleasant. It is not especially objectionable. The tannate in proportional doses is also recommended for grown people who bear the other salts of quinine badly. The writer has had no experience with it. The German plan requires less quinine. It is more uncomfortable for those taking it—at least if they bear it badly. The writer speaks from experience with himself. Plehn's

modification, 8 grains every five days, should not be ill borne, however.

All agree that where malaria is intense a larger dose is required than where it is mild. The crew of an American vessel were not protected at Tampico by 5 grains daily with an extra 5 grains Sunday, and failures have occurred even when larger doses have been given. Yet the consensus of observation is that the development of malarial fever can be prevented in the great majority of people by a dose of quinine which they can take without undue discomfort. Some people, indeed, can not take quinine at all, but they are very few. In North Carolina and probably in other Southern States the writer considers about the same malarial conditions to prevail as in Italy, and from 5 to 7 grains per day as sufficient for adults according to the intensity of the malaria in the district. Were we only considering prevention of malaria in people who were not infected it would not be necessary to begin taking quinine until the "malarial season" begins—June 1 or June 15 would probably be early enough, possibly even July 1. A considerable number of our people, however, are already infected, the malaria keeping over (latent) from the last season or maybe longer, and it would be an advantage to them to begin quinine, in as full doses as can be borne without discomfort, before the first warm weather begins—in April generally. This will quite frequently prevent the relapses which are so apt to come on in the early summer.

The use of quinine to cure malarial infections, that is, given until the blood is freed from malarial parasites, is also truly a means of malarial prophylaxis, and one of no small value. Thus used it prevents the people to whom it is administered from infecting mosquitoes and thus communicating the disease to others. This, however, is not what is usually meant by the term "quinine prophylaxis" and will not be gone into here, except to say (1) that for success it usually takes a rather long course of quinine and in fairly full doses, especially at first; (2) that the sooner treatment is begun after the beginning of the infection the better is the chance of success; and (3) that in old recurrent attacks it is much more difficult to get rid of the parasites permanently.

Summary.

(1) The use of quinine in small doses is an efficient method for preventing malarial fever.

(2) This method is especially adapted for use in a farming community where it is not practicable economically to get rid of malarial mosquitoes or to properly screen against them. This is practicable everywhere, at all times, and by almost every person.

(3) In malarious States it should be taken in doses of from 5 to 7 grains per day by grown people, 2 to 3 grains by children—less if

small—during the malarial season, say, June to November. Somewhat smaller doses will be efficient in places where the malaria is not bad. If begun in March or April, it would prevent a certain number of relapses.

(4) In these doses thus given it does no injury of any kind to those taking it and does not produce blackwater fever (hemorrhagic malarial fever) or cause such attacks of malaria as do develop to be more difficult to cure by quinine.

(5) It can be taken in these doses by almost all people without discomfort, or with discomfort for only the first 7 or 8 days. In cases where it does produce discomfort a smaller dose should be tried and, if possible, increased later. If not possible to increase the dose, even the smaller dose will lessen the chance of development of malarial fever. Craig found 2½ grains per day efficient against tertian and quartan infections. The nature of the infections in any locality can be found from the physicians.

(6) The insoluble salts of quinine are better borne—i. e., cause less discomfort—than the soluble. The tannate is the most insoluble and is said to be the best borne. Made up with chocolate and sugar into tabloids it is best suited for administration to children. As the tannate contains a smaller proportion of quinine than the sulphate, from 2 to 2½ times as much must be taken to get the same effect.

(7) When insoluble salts of quinine are recommended, it is not meant that pills or tablets which do not disintegrate when taken will do. They of course are worthless. The sulphate of quinine, which is the salt ordinarily used, is probably best taken in 2 or 3 grain tablets. Drop one of them in a glass of water and if within, say, 5 or 10 minutes it crumbles, or begins to crumble considerably, it is suitable to take. If it does not, it is not. The same test applies for pills. In general only soft pills are of any value. Quinine in capsules of course is efficient, but is rather costly if bought and troublesome if filled at home.

(8) *Cost.*—It is more economical for a community to purchase its quinine in whatever form used, by wholesale than to get it at retail. It might be handled as in Italy. Quinine sulphate is quoted wholesale in 100-ounce lots at 25 cents per ounce in bulk or 33 cents per ounce in ounce bottles. It is about 45 to 50 cents per ounce retail. Quinine 2 grain and 3 grain tablets should cost very little more than the price of the contained quinine. Quinine tannate in tablets with chocolate and sugar is offered by one American firm, the 5-grain tannate quinine tablets at \$4.10 per 1,000 tablets, and the 2-grain tablets at \$1.80 per 1,000 tablets in 100,000 lots.

(9) In addition to the use of quinine, whenever it is practicable to do so, the house should be screened, brush and high weeds near it cut away and pools and wet places drained or filled. If this last

is not practicable wet places and pools should be oiled. The drainage and filling up of wet places is a *permanent* antimalarial work, done once for all. Where they can be done they are far better than quinine prophylaxis, which must be continued year after year.

In a community using quinine prophylaxis there will still be a certain number of cases of malarial fever. Some of these will be failures of the method, but others, and the majority if it be used properly, will be relapses of previous malarial infections from the last season. In the Italian army in 1911 we have seen that there were 304 relapses and 186 new cases to 10,000 men. A certain number of these relapses are indeed prevented by quinine prophylaxis, but not all.

NOTE.—It would appear that in those sections of the United States where malaria is present and the people are as intelligent as those in the malarious districts of Italy equally good results can be obtained by the use of quinine in the prevention of malaria.—EDITOR.

CAR SANITATION.

CLEANSING AND DISINFECTION OF RAILROAD COACHES—A REPORT OF METHODS USED AT ASHEVILLE, N. C.

By A. D. FOSTER, Passed Assistant Surgeon, United States Public Health Service.

I have the honor to transmit the following report regarding the methods in use at Asheville, N. C., for the sanitation and disinfection of railroad cars as carried out by the Pullman and the Southern Railroad Cos.

In the State of North Carolina there is no State law regulating the sanitation of railroad coaches, and the measures now being carried out were instituted by the railroad companies of their own volition for the protection of the traveling public.

Disinfection of Sleeping Cars.

Upon arrival in Asheville, as soon as the passengers have disembarked, the car is shunted to a side track in the railroad yards. This track is used exclusively by cars undergoing cleaning and disinfection. On each side of the track is a platform several hundred feet long and built on a level with the floor of the car itself.

The ventilators and windows of the car are tightly closed, the berths are taken down, and blankets, pillows, and mattresses are spread out so that the formaldehyd gas may have access to the contents of the car. When this has been done, three galvanized iron pails are placed on the floor of the car, one at each end and one in the center of each car. In each pail are placed 500 c.c. of commercial formalin and 250 grams of potassium permanganate, and the doors of the car are tightly closed. The car remains closed for about 12 hours; the windows and